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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/454,334	12/03/99	HRUSKA K	BJCH 10041

000321 HM22/0620
SENNIGER POWERS LEAVITT AND ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS MO 63102

EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	8

DATE MAILED: 06/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/454,334	HRUSKA, KEITH	
	Examiner	Art Unit	
	Janet Kerr	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 March 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7,8 and 10-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7,8 and 10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

Response to Amendment

The amendment filed 3/28/01 has been entered.

Claims 3, 4, 6, and 9 have been canceled.

Claims 12-14 have been added.

Claims 1, 2, 5, 7, 8, and 10-14 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 7 and 12 are/ remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record and the reasons below.

As stated in the previous Office action, the specification does not adequately describe a nucleotide sequence comprising a sequence encoding a protein having α-ENaC activity, and wherein the sequence comprises any portion of the nucleotide sequence which has at least 80% homology with SEQ ID NO: 1, and therefore, does not provide an adequate written description of transgenic mammals comprising the nucleotide sequence.

It is argued that in view of the cancellation of claims 3 and 4, the rejection is moot (see page 4 of applicant's Response). This argument is not persuasive. As stated on page 5 of the previous Office action, as the specification does not provide a written description of the nucleic acid sequences comprising a sequence encoding a protein having α-ENaC activity, and wherein

the sequence comprises any portion of the nucleotide sequence which has at least 80% homology with SEQ ID NO: 1, the specification also does not provide an adequate written description for transgenic animals generated with the nucleic acid sequences.

Claims 1, 2, 5, 7, 8, and 10-14 are/remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record and the reasons below.

The claims are directed to transgenic non-human mammals comprising a nucleotide construct capable of enhanced expression of stretch-activated cation channel in osteoblasts relative to a wild-type littermate (claim 1), wherein the mammal is a murine (claim 2); transgenic non-human mammals which have at least one osteoblast cell which contains a recombinant DNA sequence which includes (a) the nucleotide sequence of SEQ ID NO: 1 or its complement, or any contiguous portion of the nucleotide sequence or complement which as at least 36 nucleotide residues in length, (b) a nucleotide sequence which has at least 80% homology with SEQ ID NO: 1, or (c) any contiguous portion of the nucleotide sequence of (b) which is at least 36 nucleotide residues in length, and which at least one osteoblast cell is capable of enhanced expression of stretch-activated cation channel relative to such cell without the recombinant DNA sequence (claim 5), wherein the mammal of claim 5 is a murine (claim 7), or wherein the mammal of claim 5 wherein the at least one osteoblast cell is capable of producing at least 31% more stretch-activated cation channel mRNA than such cell without the recombinant DNA sequence (claim 12), and a transgenic murine comprising a nucleotide construct capable of enhanced expression of stretch-activated cation channel in osteoblasts relative to a wild-type littermate, wherein the nucleotide construct comprises a gene encoding a stretch-activated cation channel operably linked to an osteocalcin promoter (claim 13), and wherein the osteoblast cells comprising the nucleotide construct are capable of producing at least 31% more stretch-activated cation channel mRNA than such cells without the recombinant DNA sequence. Claims 8, 10, and 11 are directed to

methods of producing transgenic mammals comprising a stretch-activated cation channel transgene.

As set forth in the Office action of 9/28/00 (Paper No. 6), the specification is non-enabling for the claimed transgenic non-human mammals or the methods of making transgenic non-human mammals comprising a stretch-activated cation channel transgene as the specification fails to provide sufficient guidance for how to make the transgene constructs which are required to generate the transgenic non-human mammals such that the stretch-activated cation channel is expressed. Moreover, generating transgenic mammals which display the desired phenotype is an unpredictable art.

Applicant's arguments filed 3/28/01 have been fully considered but they are not persuasive. It is argued that the specification provides the necessary information required to incorporate nucleotide constructs capable of enhanced expression of the stretch-activated cation channel into a mammal to generate the claimed transgenic non-human mammals (see page 5 of applicant's Response). With regard to the arguments that a variety of promoters and vector backbones may be use in the construct and the selection of these features and appropriate manipulation are well within the skill of the art, and further, that generating transgenic non-human mammals requires routine experimentation, not undue experimentation in view of the reference of Murray *et al.*, the arguments are not persuasive. Providing an appropriate vector comprising a suitable promoter operably linked to a transgene of interest to generate transgenic non-human mammals displaying a particular phenotype is not a routine or predictable art. As set forth in the previous Office action, there are numerous factors which can impact on expression of the transgene, including the species used, the design of the construct, and particularly, the promoter. As examples, Kappel *et al.* teach that while transgenes can be targeted, inherent cellular mechanisms may alter the pattern of gene expression, and Cameron teaches that "A feature common to many transgenic experiments is the unpredictable nature of transgene expression with different transgenic lines produced with the same construct frequently displaying different levels of expression". The skilled artisan could not predict, *a priori*, whether a transgenic construct (particularly with an undisclosed promoter)

would be capable of expressing the transgene in a non-human mammal. With regard to making transgenic non-human mammals for the purpose of expressing a heterologous protein of interest in the milk of the transgenic mammals (Murray *et al.*, supplied by applicant), this art is more routine as the vectors, and particularly the promoters used to make the construct for integration into the somatic and germ-line of non-human mammals, have been well characterized in a number of mammalian species. This predictability is not evident for the promoter used and claimed in the instant invention. For example, with regard to utilizing the osteocalcin promoter to direct expression of a gene encoding a protein of interest, variability of expression levels of transgene are observed with constructs comprising osteocalcin promoters (as evidenced in the teachings of Frenkel *et al.*, McCabe *et al.*, and Clemens *et al.* (See pages 9-10 of the previous Office action. From these teachings, it is apparent that the activity and inducibility of the osteocalcin promoter is not predictable as numerous variables including length of the promoter region, extrachromosomal or chromosomal localization of the exogenous promoter, inclusion or exclusion of regulatory elements, and differential species responses to trans-acting factors affect promoter activity.

Given the unpredictability in the transgenic art, it would require undue experimentation, not routine experimentation to make the claimed transgenic non-human mammals. As the only information provided by the specification is the recitation of a vector, pKBpA, which contains a nucleic acid sequence encoding α-rENaC, which is used in making the transgenic mouse, without a disclosure of how to construct such vector, it is suggested that applicant deposit the vector (see MPEP 2401 and 2402) and submit claims directed to a transgenic mouse wherein the claims include the limitations that the mouse comprises the vector, expresses the transgene in osteoblasts, and displays the particular phenotype disclosed in the instant application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5, 7, and 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, and 13 are rendered vague and indefinite by the phrase "capable of enhanced expression" as it is unclear under what conditions the nucleotide construct (or the mammal, or the osteoblast) has the capability of enhanced expression of stretch-activated cation channel, or if the nucleotide construct is in fact expressed.

Claims 12 and 14 are rendered vague and indefinite by the phrase "capable of producing" because it is unclear under what conditions the osteoblast(s) has the capability of producing at least 31% more stretch-activated cation channel mRNA, or if the mRNA is in fact produced at least at the claim-designated level.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 7, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hummler *et al.* (of record), taken with Kizer *et al.* (of record) for the reasons of record and the reasons below.

Hummler *et al.* disclose a method of generating transgenic mice carrying and expressing the α subunit of ENaC under the control of an ubiquitously expressed cytomegalovirus promoter on an αENaC knockout background by breeding homozygous and heterozygous transgenic mutant mice (see page 11710, abstract and right column, last paragraph, page 11711, under Materials and Methods, and Figure 1).

Hummler *et al.* do not teach that the transgenic mice express α-ENaC in osteoblasts. However, Kizer *et al.* disclose transfecting osteoblast-like cell lines with the expression vector pCEP4 which contains, as an insert, the full-length coding region of α-rENaC. (It is known that the vector, obtained from Invitrogen, contains the CMV promoter). The transfected cells express the transgene (see e.g., page 1014, left column, under Preparation of Transfection Vector, page 1015, right column, last paragraph, and Figure 3).

In view of the teachings of Kizer *et al.* that osteoblast-like cells transfected with an expression construct comprising the CMV promoter operatively linked to α-rENaC express the transgene, and in view of the teachings of Hummler *et al.* that the transgene construct used to generate transgenic mice comprises the CMV promoter operatively linked to α-rENaC, and is expressed in different tissues of the mice, one of ordinary skill in the art would have had a high expectation that the transgenic mice of Hummler *et al.* express, or are at least capable of expressing the α-rENaC transgene in osteoblasts at the claim-designated level, barring evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Applicant's arguments filed 3/28/01 have been fully considered but they are not persuasive. It is argued that the claimed invention is not suggested by the combination of references. It is argued that the transgenic mouse of Hummler *et al.* has reduced expression of α-rENaC, and that there is no suggestion in Hummler *et al.* of expression of α-rENaC in osteoblasts. It is further argued that there is no motivation to combine the reference of Hummler *et al.* with Kizer *et al.* (see page 7 of applicant's Response).

These arguments are not persuasive as Hummler *et al.* teach the generation of transgenic mice with increased expression of the transgene α-rENaC relative to α-rENaC knock-out mice. Although the reference of Hummer et al is silent with respect to expression of the transgene in osteoblasts, given the teachings of Kizer et al that transfected osteoblast-like cell lines comprising

a transgene construct comprising a CMV promoter operatively linked to α-rENaC (i.e., a transgene construct which has the same components as the construct of Hummler et al) expresses the transgene, one of ordinary skill in the art would have had a high expectation that the osteoblasts of the transgenic mice of Hummler *et al.* also express the transgene (enhanced expression) relative to osteoblasts cells of the a-ENaC knockout mice.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1633, at (703) 305-4051. Any administrative or procedural questions should be directed to Kimberly Davis, Patent Analyst, at (703) 305-3015. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must

conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

The CM1 Fax Center number is (703) 305-7401.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600